SHOCK SOCIETY

EXECUTIVE OFFICE • (706) 722-7511 • FAX (706) 722-7515 • E-Mail: maps@csranet.com
Sherwood M. Reichard • 1021 15th Street, Suite 9 • Augusta, Georgia 30901

January 28, 1999

Defense Technical Information Center
8725 John J. Kingman Road
Suite 0944
Ft. Belvoir, VA 22060-6218

Dear Sir or Madam,

As requested I am sending, as part of the Final Report for Grant No. N00014-98-1-0691, a copy of the proceedings and form SF298 for the Twenty-First Annual Conference on Shock and the Sixth International Cytokine Conference.

Please let me know if there is any additional information you need.

Sincerely,

Sherwood M. Reichard
Executive Director

Enclosures

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	8 Dec 98	Final 14 June 98 to 31 May 99

4. TITLE AND SUBTITLE
Conferences on Shock and Cytokines

5. FUNDING NUMBERS
N00014-98-1-0691

6. AUTHOR(S)
Sherwood M. Reichard

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Shock Society
(Reticuloendothelial Society)
1021 15th Street, Suite 9
Augusta, GA 30901

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

19990209 036

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Summary of Symposia at 21st Annual Conference on Shock held in San Antonio, TX, June 14-17, 1998.

Summary of Symposia at 6th International Cytokine Conference held in Jerusalem, Israel, October 20-25, 1998

Both Symposia were very successful. The attached summaries describe the state-of-the-art Scientific progress being made in these vital areas. Also attached are abstracts of all the papers delivered at the Symposia

14. SUBJECT TERMS			15. NUMBER OF PAGES
			16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE.	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

SHOCK SOCIETY

EXECUTIVE OFFICE • (706) 722-7511 • FAX (706) 722-7515 • E-Mail: maps@csranet.com
Sherwood M. Reichard • 1021 15th Street, Suite 9 • Augusta, Georgia 30901

January 28, 1999

Dr. Jeannine Majde
Program Officer, ONR
Office of Naval Research
Ballston Tower One, Code 335
800 North Quincy Street
Arlington, Virginia 22217-5660

RE: Grant N00014-98-1-0691

Dear Dr. Majde,

On behalf of the Scientific Program Committee, Officers and Council of the Society, I want to thank the Office of Naval Research for the support of Symposia and Awards at the Twenty-First Annual Conference on Shock, June 14-17, 1998, Hill Country Resort, San Antonio, Texas and the Sixth International Cytokine Conference, October 20-25, 1998, Jerusalem, Israel.

These meetings were very successful and attended by many scientists and physicians throughout the world. We are grateful for the support of the Department of the Navy which helped make this meeting possible.

I am enclosing a copy of *SHOCK* Volume 9 1998 supplement which contains the program and abstracts for the Shock Conference and a summary of the meeting by Mark Clemens, Program Chair.

I am enclosing a copy of *EUROPEAN CYTOKINE NETWORK* volume 9, No. 3, 1998, which contains the abstracts (pages 289-543) for the Cytokine Conference. A Summary of the Conference by Udo Junker is also enclosed.

I look forward to a continued association of the Society with the Office of Naval Research.

Sincerely,

Sherwood M. Reichard
Executive Director

SHOCK SOCIETY

EXECUTIVE OFFICE • (706) 722-7511 • FAX (706) 722-7515 • E-Mail: maps@csranet.com
Sherwood M. Reichard • 1021 15th Street, Suite 9 • Augusta, Georgia 30901

January 28, 1999

Grant Administrator
Office of Naval Research
Regional Office Atlanta
100 Alabama Street NW, Suite 4R15
Atlanta, GA 30303-3104

RE: Grant N00014-98-1-0691

Dear Sir/Madam,

This is to certify that no property was purchased under this Grant.

Sincerely,

Sherwood M. Reichard
Executive Director
Shock Society (Reticuloendothelial Society)

SHOCK SOCIETY

EXECUTIVE OFFICE • (706) 722-7511 • FAX (706) 722-7515 • E-Mail: maps@csranet.com
Sherwood M. Reichard • 1021 15th Street, Suite 9 • Augusta, Georgia 30901

January 28, 1999

Grant Administrator
Office of Naval Research
Regional Office Atlanta
100 Alabama Street NW, Suite 4R15
Atlanta, GA 30303-3104

RE: Grant N00014-98-1-0691

Dear Sir/Madam,

This is to certify that the costs of this Grant were as follows.

Twenty-First Annual Conference on Shock, June 14-17, 1998

Speaker Travel Expenses	$ 4,000
Student Travel Awards	$ 1,000

	$ 5,000

Sixth International Cytokine Conference, October 20-25, 1998

Travel Expenses, Speakers and Students	$ 5,000
Grand Total	$10,000

Sincerely,

Sherwood M. Reichard
Executive Director
Shock Society (Reticuloendothelial Society)

DEPARTMENT OF THE NAVY
OFFICE OF NAVAL RESEARCH
800 NORTH QUINCY STREET
ARLINGTON, VA 22217-5660

IN REPLY REFER TO
252:KED

SHOCK SOCIETY
1021 15TH STREET SUITE 9
AUGUSTA, GA 30901

Gentlemen:

Enclosed for your retention is one copy of Grant Number N00014-98-1-0691 which I have signed for the Government. The grant document does not require your signature.

Please acknowledge receipt of this grant by promptly signing and returning the enclosed copy of this transmittal letter to this office to the attention of ONR 252:KED. Keep this original letter for your records.

In the event of any disagreement with the grant provisions, you must notify this office within thirty (30) days of the date of this letter. If you have any questions, please contact Kathleen E. Dillard by telephone on (703) 696-4516.

Sincerely,

Diane Gales
Grants Officer

Grants Officer

Enclosure

Acknowledgement of Receipt

By: _____ Date: 5/29/98

Copy returned

The Twenty First Annual Conference on Shock

June 14-17, 1998

San Antonio Texas

Summarized by Mark Clemens, Scientific Program Chair

The Shock Society met in San Antonio in June with scientific topics hot enough to precipitate the most severe heat wave in recent memory of southern Texas! The meeting comprised two workshops, three symposia, four minisymposia, the traditional Young Investigators Award and Poster sessions for presentation of the 234 contributed abstracts as well as the usual Shock Society ambiance provided by great science in a great setting.

Sunday afternoon started with a workshop on Funding Opportunities and Strategies from the NIH. Scott Somers of NIGMS put together a superb overview of the workings of the review and award process of the NIH with contributions from Gerald Becker and Bruce Wetzel giving the perspective of Scientific Review Administrators and Ron Maier providing insight from the perspective of a study section chair.

Symposium I addressed Chemokines and Parenchymal Cell Adhesion Molecules. Hartmut Jaeschke chaired the session which explored the role these molecules which extend beyond the now established role of endothelial cell adhesion molecules in regulating neutrophil-dependent injury in shock. Wayne Smith provided an updated overview of adhesion molecules and chemokines followed by Hartmut Jaeschke's summary of specific interactions of endothelial ICAM expression and chemokine expression by hepatocytes in causing hepatocyte damage in endotoxemia. Lisa Colletti summarized her recent work on the ENA class of chemokines showing their role in normal regulation as well as a possible contributor to injury during inflammatory states. Finally, Cliff Deutschman summarized the complex regulation of chemokines in the more complex but clinically relevant model of cecal ligation and puncture.

Symposium II addressed the problem of Complexity and Non-linear Systems in Shock Research moderated by Eddy Neugebauer. This symposium confronted the non-linear nature and complexity of biological regulation and offered strategies for analyzing data related to the response to shock in terms complex systems. Speakers Christian Willy, Tim Buchman and Mark Clemens provided approaches addressed both theoretical and practical aspects of complexity and heterogeneity in Shock research.

Symposium III was best summarized by the subtitle of moderator Greg Bulkley's talk: "It ain't just reperfusion injury anymore". Speakers Heike Pahl, Pascal Goldschmidt and Csaba Szabo summarized advances indicating important signaling roles for reactive oxygen and nitrogen species from transcription to translation and post-translational modification.

The final workshop moderated by Alden Harken addressed the important question of sequential stresses in shock which can either result in protection or exacerbation. Speakers Ernest Moore, Dan Meldrum, Mohammed Sayeed, Zoltan Spolarics and Michael Bauer presented exciting new work exploring both cellular and integrative mechanisms by which the response to a stress is altered by a primary stress. This workshop highlighted the complexity of interactions

among discrete mechanisms in response to stresses associated with shock. Dr. Harken's running commentary effectively developed the theme.

The themes established by the symposia and workshops were further developed by contributed abstracts presented in minisymposia entitled *Cell Signaling, Endotoxin / Sepsis, Inflammatory Cells,* and *Preconditioning / Priming*. The future of shock research was also highlighted in the annual Young Investigator Award Session. As usual, all four presentations were winners suggesting an excellent future for Shock Research.

Congress report

2nd Joint Meeting of the International Society for Interferon and Cytokine Research and the International Cytokine Society, Jerusalem, October 25-20, 1998

by Udo Junker

Jerusalem, David's city, city of Jesus and Mohammed, holy ground for three religions, promised a unique venue for a combined meeting of the ISICR and the ICS. The meeting offered everything a scientist might want to share and receive in terms of information, and a historical background for moments of contemplation. For someone from a former communist country it was a privileged experience to walk in the steps of Jesus, or to be shown around Al Akba mosque, or to see the place David would have sacrificed his own son but for Gods word. One would need to come back and walk all these places again... The program was more centered around a few cytokines than usual - IL1, IL6, TNα and the interferons come to mind- at the same time it offered a broader perspective on their role from the point of the organism as a whole, devoting an entire session to cytokines and cancer. This short report highlights a few remarkable presentations and is not meant to give a complete review nor a ranking of scientific merit.

In his opening talk Tadamitsu Kishimoto reported on an evolving group of regulators of cytokine signaling he would call SSI's , STAT-induced STAT-inhibitors, which are also termed "SOCS". This family of 7 proteins (SSI-1 through 7) are ubiquitously expressed, with certain types being more characteristic for certain tissues, e.g. SSI7 for testis and brain. All of them feature a central SH2-domain and C-terminal SC-1 and SC-2 domains. These motifs however are necessary for activity only in certain cells such as M1 but not in others, such as COS. SSI-1 knockout mice are born more or less normal, but are 50 percent smaller than normal littermates and die within 3-4 weeks with few thymocytes, very few spleen lymphocytes and accelerated apoptosis. Presumably, base-line expression of SSI-1 silences "leaky" signalling from the JAK/STAT pathway, predominantly via STAT6.

David Goeddell of Tularik had news on TNF-related signalling. He reported on quite a number of mice with knockouts in various TNF signal mediators. Of them, TRADD $^{-/-}$ mice die at embryonic day 7, a very early stage. TRAF2 $^{-/-}$ mice fared little better with only 5% of embryos being born alive. These suffer from atrophic thymi and spleen and are much smaller with reduced cell numbers. Their thymocytes and hemopoietic cells are extremely sensitive to TNα, but not to FAS. On the other hand, they have high levels of peripheral TNF. So far, normal activation of NF*k*B and lack of activation of JNK could be shown. Of the other knockouts he described, cIAP2$^{-/-}$, NIK $^{-/-}$ and FADD $^{-/-}$ are also embryonic lethals, while Rip$^{-/-}$ are born normal and die at d3 with normal JNK activation and disrupted NF*k*B activation. Concluding he described SODD ("Silencer of death domains"), a new molecule of 60kDa interacting with TNF-receptor 1, DR3 and weakly DR4 but not TNF-R2 or FAS where it competes with TRADD for receptor binding, thus shutting down any leaky signal. After TNF binding, SODD is released from TNFR1 within five minutes, then begins re-binding the receptor after 10 minutes.

The next to speak was Michael Karin of UCSD discussing control of AP-1 and NF*k*B signalling, both being activated by IL1 binding to the IL1 receptor complex (consisting of IL1R1, MyD88, IRAK1, TRAF6). TRAF2 and TRAF6, oligomerizing, co-precipitate and activate MEKK1. MEKK1 activation leads to activation of JNKK1 and later JNK1 itself triggering AP-1 which quote "spends most of its life in the nucleus". In a parallel process IKKa and IKKb heterodimers are regulated by IKKg1 and IKKg2, differently processed products of one gene, which being devoid of intrinsic enzymatic activity, recruit kinases to activate IKKa/IKKb. This signal might be MEKK1, so that NIK is possibly not the (only) activator of IKK. This is underlined by the fact that in his system the presence of the C-terminal part of IKKg is absolutely necessary for IKK activation. In a comment following his talk, a comparable, non-enzymatic role of RIP in the activation of JNK was proposed.

A talk on the role of STAT1 in c-myc activation was given by Chilakamarti Ramana of Cleveland University. He found that in $STAT1^{-/-}$ fibroblasts, c-myc is induced about 7-fold by IFN*g*, showing that this effect is independent of STAT1. Moreover, he found that EGF was mitogenic only in cells where it did not activate STAT1, and that IFN*g* is able to abrogate PDGF-induced activation of c-myc only in normal, but not $STAT1^{-/-}$ fibroblasts. On the contrary, these latter cells show myc induction within 30 minutes and a proliferative response to IFN*g*. He could show that a consensus GAS element at around -1100nt of the myc promoter is responsible for this effect, and that the C-terminal region of STAT1 is required for it to be active.

Charles Sherr of St.Judes (Memphis) summarized data on the ARF/p53 pathway of cell cycle regulation. Specifically he investigated INK4A/p16, generally ascribed a role cell cycle arrest. He found that "conventional" $p16^{-/-}$ mice are quite normal, but show extramedullary hematopoiesis, their fibroblasts do not senesce in culture and they are tumor-prone. He could show that this effect was in fact due to lack of the product of a second, alternative reading frame, "ARF" for "alternative reading frame". The ARF gene is much larger than that of p16 and partially overlaps, using part of the 3rd exon of p16 in an out-of-frame manner. $ARF^{-/-}$, p16wt mice show all the abnormalities having been reported earlier for $p16^{-/-}$. ARF forms dimeric or trimeric complexes with p53 and mdm2 and mediates control of hyperproliferative, potentially oncogenic signals, as shown by the fact that MYC transgenic MEF rapidly activate p53/ARF complexes leading to p53 gene expression regulation and replicative crisis, and all the surviving cells being either p53 or ARF mutant. He concluded that more or less all effects earlier ascribed to p16 are really ARF-mediated.

Anita Roberts of NCI, Bethesda discussed TGF β signalling via SMADs. Today at least nine SMADs are out there, sharing the same principles of internal structure, namely two MAD-homology domains (one of them may be absent as in the inhibitory SMAD6 and 7) with an interspaced linker. They do have different effects on transcription however,

SMAD 1,2,3,5,8 being activators, SMAD4 a mediator and SMAD 6 and 7 being inhibitive with respect to gene transcription. A pathway resembling the STAT story seems to be evolving with SMAD 2 and 3 becoming phosphorylated by activated TGF β receptor whereupon they bind SMAD 4, translocate to the nucleus, bind DNA and regulate transcription. She stated that SMAD4 also participate in signalling from in HGF and EGF receptors, where they are phosphorylated by MEK1 which is not the case in TGF β signaling. Further she reported on a novel 27kDa melanocyte-specific protein binding to SMAD4 which has no DNA-binding activities of its own but is a strong transactivator leading to the expression of endothelin and FGF in certain cell lines while suppressing ras and E1A. This protein supposedly also interacts with CBP/p300, CREB, NF-*k*B, STAT and AP-1 and might be able to compete with them for DNA binding.

Michael Kracht of the University of Hannover, Germany reported on JNK in the induction of IL6 and IL8 by IL1. He found that there are several independent ways to induce IL8, due to AP-1, NF-*k*B and NF-IL6 binding sites in the IL8 promoter. One of these ways was via MKK7-SAPK/JNK, another from MKK6 via p38 and the third from NIK via NF-*k*B. He also reported the half life of IL8 mRNA to be around 30minutes in unstimulated cells, MKK6 having a strong stabilizing effect.

Matthew Fenton of Boston investigated the way CK-II and the downstream substrate, the transcription factor PU.1, was activated by MAPK. Using the MEK1 inhibitor PD98059 and the SAPK inhibitor SB203580 he showed that LPS signals CK-II / PU.1 activation exclusively via the MEK1-ERK1 pathway without involvement of SAPK/JNK. He was careful to state that CK-II however is not directly activated by any investigated MAPK.

Peter Krammer from Heidelberg shed some new light on relatives of the TNFR and their signal pathways. Amongst others he reported on a new apoptosis inhibitor he called FLIP (an alternative name is FLAME), a caspase-8-homolog without an enzymatic site that prevents excessive caspase 8 activation. He illustrated the role of FLIP and other intracellular regulators of CD95 with the observation that d1-peripheral blood lymphocytes are 95% CD95 positive but resistant to apoptosis, while d6-PBL are still 95% CD95 positive but strongly prone to apoptosis. He observed that during this period the inhibitory form of FLIP and bcl-Xl slightly decreased while the pro-apoptotic cFLIPp43, FADD and caspase 8 strongly increased permitting efficient DISC formation. Also he reported that in his hands all tested cytostatics from a certain threshold level induced FAS in tumor cells coinciding with cell death, but only in cell retaining wild-type p53.

Adi Kimchi extended her previous reports on death-associated proteins (DAP) in interferon α effects. The "Death-associated protein kinase", DAPK, seems to signal downstream of caspase 8 but upstream of caspase 3. Remarkably DAPK is lost in many cancers, and its expression or absence correlate with a lower or higher metastatic potential, respectively. The effect of DAPK is p53-dependent. Another DAP she found is

DAP-5/p97, a homolog of the eIF4G, a substrate for caspases. Cleavage of p97 by caspases to p86 might permit it to bind to eIF4A thus leading to CAP-independent translation of RNA.

William Paul of the NIAID, Bethesda, reported on FRIP (also "dok-2" for its homology to dok-p62), a novel cytokine-activated ras-GAP-binding protein able to inhibit proliferative responses. FRIP is involved in the signalling of the IL4-receptor, and also it becomes phosphorylated after binding of IL2, IL3 and insulin to their respective receptors. By binding to and stimulating ras-GAP it leads to reduced activation of MAPK. The gene for FRIP is located at mouse chromosome 14 near a locus called "hr" (for hairless) which develop leukemia at about 3months of age. In these mice FRIP is underexpressed. In T-cells and myeloid cells, FRIP prevents over-reaction to the cytokines mentioned above so that its absence might further leukemogenesis in these mice. Presumably the lack of ras activation by IL4 can be explained by the presence of elevated concentrations of FRIP.

I. Rooney from LIAI, LaJolla, described another member of the steadily growing TNF/TNFR family called LIGHT, a merciful acronym for "**L**ymphotoxin-like **i**nducible surface protein competing with **g**pD of herpes virus that binds the **H**VEM [herpes virus entry mediator] on **T**- and B-cells". Like all TNF-related proteins LIGHT homotrimerizes. Besides HVEM, it also binds LT- α 3 but not LT α 1β2 or TNFα. It has around 30% sequence homology to LTα, FAS and LTα. Interestingly, as does TNFα in certain cell lines, it synergizes with IFNγ in killing HT29 cells.

Keiko Ozato, NICHD Bethesda gave a very inspiring talk about histone acetylation and deacetylation in the regulation of gene expression. It is timely to consider that, amongst all those fancy transcription factors, the condition the chromatin, namely loosely knitted after action of acetylases or tightly spun around nucleosomes after deacetylation of histone, is of critical relevance for DNA accessibility. In fact, the histone acetylases PCAF and CBP are components of the ISRE complex conferring high acetylating activity and thus high transcriptional activity. As chromatin acetylation seem to be both critally dependent on and influencing the gene-regulating activity of interferons it might be warranted to check for different acetylation states in tissues with critically differing responsiveness to interferons such as interferon-responsiveness of tumors.

Bryan Williams of the Cleveland Clinic elucidated the role of protein kinase R (PKR) in interferon-mediated mechanisms of immunity. Activation of PKR is necessary for IFN to signal NF-*k*B, IRF1 and STAT3. The process of unfolding PKR is induced within 15 minutes after application of poly(IC) to cells and reaches maximal values after 2 hours, coinciding with activation of NF-*k*B by degradation of I*k*Bα. PKR$^{-/-}$ mice show impaired responses to interferons and poly(IC), such as decreased activation of NF-*k*B, IRF1 and lack of apoptosis in MEF upon exposure to poly(IC). Interestingly, PDGF signalling to c-

fos is also impaired, presumably due to the decreased synthesis of STAT3. Also, fibroblasts from these mice are Fas-resistant.

The last interleukin classified so far has number 18 and was the theme of Charles Dinarello's (Denver) talk. IL18 is a completely β-pleated structure resembling IL1. Like IL1, it is activated by an ICE-like enzyme, in this case at $D_{37}Y$. It is suspected that IL18 may have a crucial role in inflammation as it is capable of inducing TNFα and ICAM-1, on the other hand it is known to induce IFNg; the reported pro-IFN effect of IL12 in Th1 cells is in fact due to the induction of the IL18-receptor. The holoreceptor consists of two chains, the signalling IL18Ra and IL18Rb of which there exists a soluble form; as in the case of IL1 there also exists a soluble decoy receptor IL18RB. The IL18-receptor strikingly resembles the IL1-receptor insofar as it binds to an signals via MyD88, IRAK, TRAF6. The capability of LPS to induce IL8 and IL1beta is crucially dependent on the production of IL18, to be cleaved by ICE, and the presence of TNFα permitting IL18 to induce IL1β and IL8.

IL18 also was the topic of Giamila Fantuzzi, also from the group in Denver. One of the major activators of IL18 is PR3, a serine protease for which there are two cleavage sites in human IL18 and four in murine IL18. PR3 is principally a cytoplasmic protein which translocates to the membrane upon activation by cytokines within 5 minutes. PR3 might be the most prominent activator of (staphylococcus-induced) IL18 as its inhibitor CE-2072 leads to cessation of production of IFNg while leaving ICE activity untouched. ICE activity on the other hand is necessary for TNF-induced IL18. This observation is quite remarkable as PR3 is the target of c-ANCA autoantibodies found in Wegener's granulomatosis, a severe disease with a strong component of dysregulation of cellular interaction.

More on IL-18 was contributed by Daniela Novick, describing a soluble competitive IL18-binding protein of ≈40kDa. IL18BP shares 65% homology with its human counterpart. The latter exists in at least 3 splice variants from 4 exons, the gene spanning some 8 kbp. It is not clear whether IL18BP is the shed product of an IL18-receptor since no transmembrane domain has been identified in its sequence.

Meanwhile, some of the IL18 signalling pathways have been elucidated as shown by Dr. Kauschat from Frankfurt. He found that in NK-92 cells, IL18 activated STAT3 but not STAT5 within 5 minutes. In parallel, IL18 predominantly activated ERK2 and more weakly ERK1.

Joost Oppenheim presented information on some proteins one would not usually take for chemokines. One of them, the protease Cathepsin G, is a constitutive part of the neutrophil's granules. As it turns out it is tremendously chemotactic, most likely acting via CXCR6 and / or fMLP-R; at 0.5μg/ml it is more effective than fMLP itself. Incidentally, Cathepsin G is capable of cleaving fMLP yielding another very potent

chemotactic peptide of 19 amino acids. Another faux chemokine is one of the acute-phase-proteins, serum amyloid A. Binding to the low-affinity fMLP-receptor it triggers calcium influx, desensitizes the receptor to fMLP and induces neutrophil adhesion to vascular endothelial cells. As SAA and fMLP show exactly opposite effects on low- and high-affinity fMLP-R it might be assumed that the la-fMLP-R is in a SAA-receptor by its primary function.

Over the years both participating societies have established traditions of awarding promising scientists various prizes. Congratulations to the ICS awardees: Young investigator - A.Krause and X.Ma; postdoctoral investigator - M.N.Devalaraja; outstanding scholar - F.Osman, L.P.Cousens and V.Shankaran.

Taken together, the participants left the meeting inspired by the science brought together in a remarkable event by (and many thanks to them!) Raymond Kaempfer, Michel Revel, David Wallach and Isaac Witz. Major and minor contributions illustrated the progress of the cytokine story, sometimes slow, sometimes with astonishing insights. And for those who would not be satisfied by science, the meeting venue, the city and country gave their utmost.

The next meeting of the ICS will be held December 5-9, 1999 at the Hyatt Regency Hilton Head, Hilton Head Island, South Carolina and will be organized by Scott Durum, Jan Vilcek, Ann Richmond and Bruce Beutler.

REPORT OF INVENTIONS AND SUBCONTRACTS

(Pursuant to "Patent Rights" Contract Clause) (See Instructions on Reverse Side.)

Form Approved
OMB No. 0704-0297
Expires Jun 30, 1992

1a. NAME OF CONTRACTOR/SUBCONTRACTOR	c. CONTRACT NUMBER	2a. NAME OF GOVERNMENT PRIME CONTRACTOR	c. CONTRACT NUMBER	3. TYPE OF REPORT (X one)
Shock Society		Office of Naval Research	N0001 4-98-1-0691	a. INTERIM [X] b. FINAL
b. ADDRESS (Include ZIP Code)	d. AWARD DATE (YYMMDD)	b. ADDRESS (Include ZIP Code)	d. AWARD DATE (YYMMDD)	4. REPORTING PERIOD (YYMMDD)
				a. FROM June 98
				b. TO May 99

SECTION I – SUBJECT INVENTIONS

5. "SUBJECT INVENTIONS" REQUIRED TO BE REPORTED BY CONTRACTOR/SUBCONTRACTOR (If "None," so state)

a. NAME(S) OF INVENTOR(S) (Last, First, MI)	b. TITLE OF INVENTION(S)	c. DISCLOSURE NO., PATENT APPLICATION SERIAL NO. OR PATENT NO.	d. ELECTION TO FILE PATENT APPLICATIONS				e. CONFIRMATORY INSTRUMENT OR ASSIGNMENT FORWARDED TO CONTRACTING OFFICER	
			(1) United States		(2) Foreign			
			(a) Yes	(b) No	(a) Yes	(b) No	(1) Yes	(2) No
None	None							

f. EMPLOYER OF INVENTOR(S) NOT EMPLOYED BY CONTRACTOR/SUBCONTRACTOR		g. ELECTED FOREIGN COUNTRIES IN WHICH A PATENT APPLICATION WILL BE FILED	
(1) (a) Name of Inventor (Last, First, MI)	(2) (a) Name of Inventor (Last, First, MI)	(1) Title of Invention	(2) Foreign Countries of Patent Application
(b) Name of Employer	(b) Name of Employer	None	
(c) Address of Employer (Include ZIP Code)	(c) Address of Employer (Include ZIP Code)		

SECTION II – SUBCONTRACTS (Containing a "Patent Rights" clause)

6. SUBCONTRACTS AWARDED BY CONTRACTOR/SUBCONTRACTOR (If "None," so state)

a. NAME OF SUBCONTRACTOR(S)	b. ADDRESS (Include ZIP Code)	c. SUBCONTRACT NO.(S)	d. DFAR "PATENT RIGHTS"		e. DESCRIPTION OF WORK TO BE PERFORMED UNDER SUBCONTRACT(S)	f. SUBCONTRACT DATES (YYMMDD)	
			(1) Clause Number	(2) Date (YYMM)		(1) Award	(2) Estimated Completion
None	None						

SECTION III – CERTIFICATION

7. CERTIFICATION OF REPORT BY CONTRACTOR/SUBCONTRACTOR (Not required if [ ] Small Business or [ ] Non-Profit organization.) (X appropriate box)

a. NAME OF AUTHORIZED CONTRACTOR/SUBCONTRACTOR OFFICIAL (Last, First, MI)	c. I certify that the reporting party has procedures for prompt identification and timely disclosure of "Subject Inventions," that such procedures have been followed and that all "Subject Inventions" have been reported.	
Reichard, Sherwood M		
b. TITLE	d. SIGNATURE	e. DATE SIGNED
	Sherwood Reichard	8 Dec 99

DD Form 882, OCT 89 *Previous editions are obsolete.* 971/284

FINANCIAL STATUS REPORT

(Follow instructions on the back)

1. FEDERAL AGENCY AND ORGANIZATIONAL ELEMENT TO WHICH REPORT IS SUBMITTED: Office of Naval Research	2. FEDERAL GRANT OR OTHER IDENTIFYING NUMBER: N00014-98-1-0691	OMB Approved No. 80-R0180	PAGE OF PAGES
3. RECIPIENT ORGANIZATION (*Name and complete address, including ZIP code*): Shock Society (Res Society) 1021 15th Street, Suite 9 Augusta, GA 30901	4. EMPLOYER IDENTIFICATION NUMBER	5. RECIPIENT ACCOUNT NUMBER OR IDENTIFYING NUMBER	6. FINAL REPORT ☐ YES ☐ NO	7. BASIS ☐ CASH ☐ ACCRUAL
	8. PROJECT/GRANT PERIOD (*See instructions*) FROM (*Month, day, year*): June 14, 1998 — TO (*Month, day, year*): May 31, 1999	9. PERIOD COVERED BY THIS REPORT FROM (*Month, day, year*): June 14, 1998 — TO (*Month, day, year*): May 31, 1999	

10. STATUS OF FUNDS

PROGRAMS/FUNCTIONS/ACTIVITIES ►	(a)	(b)	(c)	(d)	(e)	(f)	TOTAL (g)
a. Net outlays previously reported	$	$	$	$	$	$	$ 9,000
b. Total outlays this report period							1,000
c. *Less:* Program income credits							
d. Net outlays this report period (*Line b minus line c*)							1,000
e. Net outlays to date (*Line a plus line d*)							10,000
f. *Less:* Non-Federal share of outlays							Ø
g. Total Federal share of outlays (*Line e minus line f*)							10,000
h. Total unliquidated obligations							
i. *Less:* Non-Federal share of unliquidated obligations shown on line h							
j. Federal share of unliquidated obligations							
k. Total Federal share of outlays and unliquidated obligations							
l. Total cumulative amount of Federal funds authorized							10,000
m. Unobligated balance of Federal funds							Ø

11. INDIRECT EXPENSE	a. TYPE OF RATE (*Place "X" in appropriate box*) ☐ PROVISIONAL ☐ PREDETERMINED ☒ FINAL ☐ FIXED	b. RATE	c. BASE	d. TOTAL AMOUNT	e. FEDERAL SHARE

12. REMARKS: *Attach any explanations deemed necessary or information required by Federal sponsoring agency in compliance with governing legislation.*

13. CERTIFICATION

I certify to the best of my knowledge and belief that this report is correct and complete and that all outlays and unliquidated obligations are for the purposes set forth in the award documents.

SIGNATURE OF AUTHORIZED CERTIFYING OFFICIAL

DATE REPORT SUBMITTED: 8 Dec 98

TYPED OR PRINTED NAME AND TITLE: Sherwood M. Reichard, Executive Director

TELEPHONE (*Area code, number and extension*): 706-722-751

269-101

STANDARD FORM 269 (7-76)
Prescribed by Office of Management and Budget
Cir. No. A-110

REQUEST FOR ADVANCE OR REIMBURSEMENT

(See instructions on back)

Budget, No. 80-R0183 | PAGES

1. TYPE OF PAYMENT REQUESTED — a. "X" one, or both boxes: ☐ ADVANCE ☐ REIMBURSEMENT; b. "X" the applicable box: ☐ FINAL ☐ PARTIAL

2. BASIS OF REQUEST: ☐ CASH ☐ ACCRUAL

3. FEDERAL SPONSORING AGENCY AND ORGANIZATIONAL ELEMENT TO WHICH THIS REPORT IS SUBMITTED	4. FEDERAL GRANT OR OTHER IDENTIFYING NUMBER ASSIGNED BY FEDERAL AGENCY	5. PARTIAL PAYMENT REQUEST NUMBER FOR THIS REQUEST
office of Naval Research	N00014-98-1-0691	2

6. EMPLOYER IDENTIFICATION NUMBER	7. RECIPIENT'S ACCOUNT NUMBER OR IDENTIFYING NUMBER	8. PERIOD COVERED BY THIS REQUEST: FROM (month, day, year)	TO (month, day, year)
		June 14, 1998	May 31, 1999

9. RECIPIENT ORGANIZATION	10. PAYEE (Where check is to be sent if different than item 9)
Name: Shock Society (Reticuloendothelial Society)	Name: Same
Number and Street: 1021 15th Street, Suite 9	Number and Street:
City, State and ZIP Code: Augusta, GA 30901	City, State and ZIP Code:

11. COMPUTATION OF AMOUNT OF REIMBURSEMENTS/ADVANCES REQUESTED

PROGRAMS/FUNCTIONS/ACTIVITIES ►	(a)	(b)	(c)	TOTAL
a. Total program outlays to date (As of date)	$	$	$	$ 10,000
b. *Less:* Cumulative program income				Ø
c. Net program outlays (*Line a minus line b*)				10,000
d. Estimated net cash outlays for advance period				Ø
e. Total (*Sum of lines c & d*)				10,000
f. Non-Federal share of amount on line e				Ø
g. Federal share of amount on line e				10,000
h. Federal payments previously requested				9,000
i. Federal share now requested (*Line g minus line h*)				1,000
j. Advances required by month, when requested by Federal grantor agency for use in making prescheduled advances — 1st month				
2nd month				
3rd month				

12. ALTERNATE COMPUTATION FOR ADVANCES ONLY

a. Estimated Federal cash outlays that will be made during period covered by the advance	$ 1,000
b. *Less:* Estimated balance of Federal cash on hand as of beginning of advance period	Ø
c. Amount requested (*Line a minus line b*)	$ 1,000

13. CERTIFICATION

I certify that to the best of my knowledge and belief the data above are correct and that all outlays were made in accordance with the grant conditions or other agreement and that payment is due and has not been previously requested.

SIGNATURE OF AUTHORIZED CERTIFYING OFFICIAL	DATE REQUEST SUBMITTED
Sherwood Reichard	8 Dec 1998
TYPED OR PRINTED NAME AND TITLE: Sherwood M. Reichard, Executive Director	TELEPHONE (AREA CODE, NUMBER, EXTENSION): 706-722-7511

This space for agency use